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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,101	BRENNER, SYDNEY	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 4/19/05. Claim 1 was amended in the response, and claims 5-20 have been canceled. Claims 1-4 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

Drawings

2. Figure 7B is objected to because it is difficult to read, much of the illustrated electropherogram is a large black blur. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the

applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

3. The corrections to the other drawings are approved.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims have been amended, and they remain unclear with regard to the polymorphic consensus sequence. The claimed library has fragments that are "portions" of a consensus sequence. The consensus sequ3nce is "the sequence obtained by aligning the sequences of said pooled DNA to provide maximum homology." However, this is not clear. It is not clear how a sequence is "obtained" by simply aligning a pooled DNA from five individuals. The definition of the polymorphic consensus sequence is not clear because it is not clear what it means to align "pooled DNA" because "pooled DNA" appears to refer to actual DNA molecules yet the "aligning" step appears to be a step of data manipulation. The claims are entirely unclear as to how the definition of the consensus sequence is structurally limiting to the claimed library as these are process limitations that define how the product could be identified, but it is not clear what they mean with regard to the structure of the claimed product.

Furthermore, it is not clear what it means for the library to be "enriched" for a particular type of fragments relative to one another. It is not clear if that means, for example, that there are more of fragments of type (a) than type (b) in a sample or if a product which has less fragments of type(a) than type (b) could be within the scope of this "enrichment." An example of the latter would be, for example, a library that begins with far more fragments of type (b) than type (a) and some of the fragments of type (b) are removed, but still there remain more fragments of type (b) than type (a). Is this type of library "enriched" for type (a) relative to type (b)? The specification does not define this enrichment, and therefore the library encompassed within the scope of these claims is not clear.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 1 is rejected under 35 U.S.C. 102(b) and 102(a) as being anticipated by Pierard *et al.* (Journal of Clinical Microbiology, Nov. 1998, p. 3317-3322), as evidenced by GanBank AF043627.

This application claims priority to two provisional applications. A review of these applications by the examiner did not identify support for the instantly claimed invention in the provisional applications. For example, no descriptive support for the limitations of claims 1-4 which refer to or describe the polymorphic consensus sequence was located. With regard to

claims 13 and 14, no basis was identified for the "forming a proper subset" limitation in claim 13 or the limitations which refer fragments of "the same locus" in both claims. Therefore, the priority date of the instantly rejected claims is determined to be the instant filing date and the reference is available under 102(b). Nonetheless, the reference is also available under 102(a) as of even the earliest possible filing date. In the event that applicant is able to establish priority for the instantly claimed invention to one or both of the provisional applications the rejection under 102(b) will be withdrawn but the rejection under 102(a) will remain.

With regard to claim 1, Pierard *et al.* teach a nucleic acid library comprising a heterogeneous mixture of nucleic acid fragments wherein each fragment is a portion of a polymorphic subregion of a polymorphic consensus sequence. The polymorphic subregion is bounded on each end by a first restriction site "s", present in each of said pooled DNA sequences, and contains an internal second restriction site t, different from said first restriction side, in some but not all of said pooled DNA sequences.

Pierard *et al.* amplify a portion of the E. coli genomes that comprises polymorphic restriction sites. The amplified fragments are from a sample of E. coli which inherenltly comprises DNA from at least five individuals in a population wherein each individual is a separate cell of the E. coli culture. The fragments in the amplified library taught by Pierard *et al.* are a portion of a polymorphic subregion bounded on each end by a first restriction site "s", present in each of said pooled DNA sequences, and contains an internal second restriction site t, different from said first restriction side; in some but not all of said pooled DNA sequences. For example, Pierard *et al.* amplify sample using primers VT2-e and VT2-f in order to amplify nucleic acid that comprises polymorphic HaeIII and PvuII sites (see Table 2 and p. 3318). These

primers amplify a portion of DNA that comprises the following sequence (numbering and sequence as in GenBank AF043627, enclosed herein and referred to in Pierard *et al.* at page 3318)

1059-aa tactttatgg gaaagtaata ccgcagctgc ttttctgaat cgcagggctc actctttaaa tacatccgga gaataacggg agttaaatat gaagaagata tttgtagcgg ctttatttgc ttttgtttct gttaatgcaa tggcagctga ttgtgcaaaa ggtaaaattg agttctctaa gtataatgag aatgatacat tcacagtaaa agtggccggg aaagagtact ggactaaccg ctggaatctg caaccgctac tgcaaagcgc acagttaaca ggaatgacgg taacaatcaa atcaaatacc tgtgcgtcag gttcaggatt tgctgaagtg cagttta-1407

This amplified portion comprises a polymorphic restriction site PvuII, for example beginning at nucleotide 1204 in the sequence recited above. Within the larger sequence, from which this fragment was amplified, this fragment was bounded on each end by a first restriction site "s" since the larger sequence has AcuI sites that begins at position 137 and 1414 of the sequence (see the GenBank record). Thus, the portion amplified by Pierard et al. is a portion of a polymorphic subregion as defined by the claim. The library of amplified fragments is entirely composed of portions of polymorphic subregions since only portions of polymorphic subregions are amplified.

Therefore the teachings of Pierard *et al.* anticipate the rejected claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ausubel et al. WO 95/25538 in view of Arnheim et al. (PNAS, 1985, Vol. 82, p. 6970-6974).

Ausubel *et al.* teach a nucleic acid reference library comprising a heterogenous mixture of nucleic acid fragments wherein each fragment

(a) is a portion of a polymorphic subregion of a polymorphic consensus sequence derived from said pooled DNA or (b) is derived from a non-polymorphic subregion,

each of said polymorphic subregions is bounded by first restriction sites and comprises an internal polymorphic restriction site which is different from said first site;

and said library is enriched for fragments of type (a) relative to type (b).

Example XI taught by Ausubel *et al.* (beginning on page 59) teaches a method for cloning polymorphic restriction fragments. Namely, turning to figure 9 taught by Ausubel *et al.*, section 9D and 9E both provide a library which is enriched for fragments that are portions of polymorphic subregions of organism A compared to organism B. For example, in the library of nucleic acids in figure 9D, the fragment 5' which was present in both organism A and organism B is not present in the library since enrichment steps were applied that resulted in the exclusion of fragments that were common to both organisms. In the library of nucleic acids in figure 9E is entirely comprised of sequences that comprise a portion of a subregion of a polymorphic consensus sequence and are bounded by first restriction sites.

With regard to the limitations within claim 1 that require that the sequences are portions of a "polymorphic consensus sequence" that is obtained by aligning the sequence so said pooled DNA to provide maximum homology, as noted in the previous rejections under 112 2nd paragraph, it is not clear how an actual nucleic acid sequence can obtained by aligning

information. Further, and to the point for this rejection, it is not clear what structural limitations are added to the claim by requiring that the fragments within the claimed library are fragments of a sequence obtained by aligning pooled sequences.

With regard to claim 2, the fragments in the libraries taught by Ausubel *et al.* comprise oligonucleotide tags (referred to therein as adaptors) and different fragments are linked to different oligonucleotide tags (in Figure 9D, for example).

With regard to claim 3, Ausubel *et al.* teach cloning the isolated sequences, a step which inherently comprises putting the fragments of the library into a repicable vector (p. 60, lines21-22).

Ausubel et al. do not teach a library that was derived from pooled DNA from at least five individuals in a population.

Arnheim et al. teach the use of pooled DNA samples to study polymorphic restriction fragments and human disease. Arnheim et al. use pools of DNA samples from 31 unrelated controls and 21 diabetic individuals to identify polymorphic restriction sites in either of the pooled samples.

It would have been prima facie obvious to one of ordinary skill in the art to have modified the libraries taught by Ausubel et al. so as to have used pooled samples as taught by Arnheim et al. to identify polymorphic restriction sites that may differ between diseased and control patients instead of the samples from "individuals" as discussed in the examples and figures in Ausubel et al. One would have been motivated to use the pooled samples by the success of Arnheim et al. in finding informative RFLP using the pooled samples and by their discussion which highlights that the identification of "informative polymorphisms by the pool

method would require only 1/N times as much effort an DNA, where N is equal to the pool size" as compared to the screening of individuals to identify the polymorphisms.

10. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ausubel *et al.* in view of Arnheim et al., as applied to claims 1-3 above, and further in view of Brenner (US 5604097).

The teachings of Ausubel et al. are discussed in the previous rejection, and are applied in this rejection to claim 4.

With regard to the limitations of claim 2, from which claim 4 depends, the fragments in the libraries taught by Ausubel *et al.* comprise oligonucleotide tags (referred to therein as adaptors) and different fragments are linked to different oligonucleotide tags (in Figure 9D, for example). Ausubel *et al.* do not teach libraries wherein the tags comprise sequences as described within claim 4.

Brennan teaches oligonucleotide tags comprised of subunits from a minimally cross-hybridizing set as described in claim 4 (see Col. 6-9, for example). Brennan teaches that these tags are useful to provide a system for tagging and sorting many thousands of fragments for simultaneous analysis and/or sequencing (Col. 3, lines 3-8). Brennan exemplifies the use of these tags for labeling restriction fragments (See example 2, Col. 24).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Ausubel *et al.* so as to have included the use of oligonucleotide tags such as those taught by Brennan instead of the tags used by Ausubel et al. One would have been motivated to utilize the tags taught by Brennan in order to take advantage of the express benefits of the methods taught by Brennan for sorting and

analyzing complex mixtures of nucleic acid sequences. Therefore in view of the teachings of the prior art, the instant invention is prima facie obvious.

Response to Remarks

112 2nd paragraph

New 112 2nd paragraph rejections are set forth to address the amendments to the claims.

Regarding the maintained rejection over the "enriched" portion of claim 1, Applicant refers to portions of the specification in an attempt to clarify what it means for the library to be "enriched" for fragments of type (a) relative to type (b). However, consideration of applicant's remarks and the portions of the specification only serve to highlight the problematic nature of the claim language. It appears from the definition of the specification and from applicant's remarks whether or not the "enriched" library is present is entirely dependent on an undefined, unclaimed starting material which contains fragments that were "selected against" as described in the specification at page 8, line 9. Applicant clearly states in the remarks that "This does not require that there are more fragments of type (a) than (b) in the library, or vice versa)." Thus, the use of the phrase "enriched" itself is the use of an entirely relative phrase whose meaning is unclear absent any standard for comparison. The rejection is maintained.

Art Rejections

The rejection in view of Ausubel et al. under 102(b) was overcome by amendment. Likewise the 103 rejection in under of Ausubel et al. in view of Brennan is overcome by amendments. New art rejections under 103 in view of these references with an added reference have been set forth. The arguments set forth regarding these rejections are thus moot.

The rejection under 102(a) and 102(b) in view of Pierard et al. has been modified to address the amendments to the claims. The rejection addresses applicant's arguments regarding the polymorphic site "s" by which the polymorphic region is bounded. The rejection sets forth that the library taught by Pierard et al. has within it "portions" of a polymorphic subregion as required in the claim. Thus, the rejection is maintained for claim 1.

Conclusion

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

July 7, 2005